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A Novel Metal Iodide Promoted Three-Component Synthesis of Substituted Pyrrolidines

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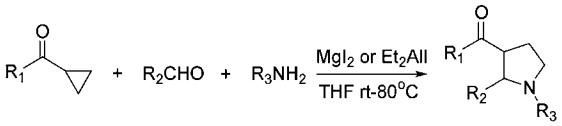
ABSTRACT



A new one-pot procedure for the synthesis of substituted pyrrolidine derivatives with commercially available cyclopropyl ketones, aldehydes, and amines by a metal iodide promoted three-component reaction was developed.

Pyrrolidines play important roles in the drug discovery process.[1] Several polysubstituted pyrrolidines have shown very potent activities as enzyme inhibitors, agonists, or antagonists of receptors.[2] Furthermore, the advanced progress achieved in genomic research increases the demand for identification of small molecules that are active and selective against a broader range of therapeutical targets. In the perspective of more biologically interesting targets becoming available, the efficient synthesis and optimization of new drug-like chemical entities actually constitutes the bottleneck in medicinal chemistry.[3]

Taking advantage of the functional assay technology R-SAT™,[4] enables exploration of an enormous range of possible drug targets in a nonbiased manner. Within this context, we have initiated a research program aimed at the development of the efficient synthesis of drug-like compounds by multicomponent reactions (MCRs).[5] Recent activities in the field prompted us to disclose parts of our findings concerning a novel three-component reaction.

Ring opening of cyclopropyl ketones with metal iodides affords attractive synthetic intermediates incorporating a nucleophile (i.e. metal enolate) and an electrophile (i.e. alkyl iodide) within the same molecule **Ia** (Scheme 1). Oshima and co-workers reported the formation of acyltetrahydrofurans by trapping metal enolates derived from cyclopropyl ketones with aldehydes.[6] Encouraged by those results we envisioned that replacing the aldehydes with imines would be an efficient way to synthesize pyrrolidines. Recently, Carreira and co-workers reported ring expansion reactions of a cyclopropanecarboxamide with aldimines in the presence of MgI_2.[7] Inspired by Carreria's work, Lautens et al. found,

(1) A search on the pyrrolidine moiety in the MDDR (MACCS-II Drug Data Report) database gave over 11 000 hits. The database is available from MDL Information Systems Inc., San Leandro, CA 94577 and contains biologically active compounds in the early stages of drug development.

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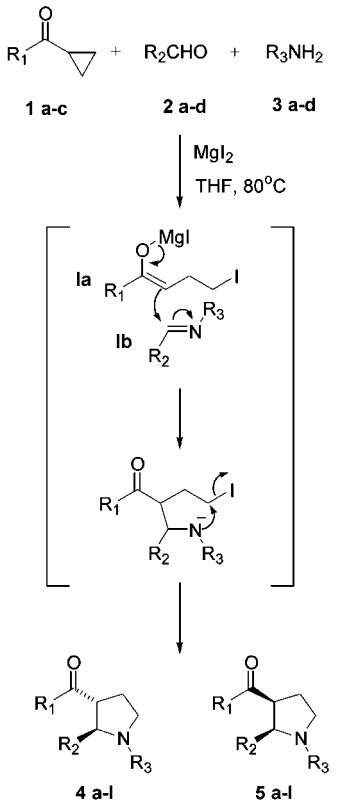
Table 1. MgI_2 Promoted Three-Component Reaction[a]

entry	R_1	R_2	R_3	product[b]	yield[c] (%)	dr[d,e] (anti:syn)	purity[f] (%)
1	Ph (**1a**)	*p*-FC_6H_4 (**2a**)	$CH_3C_6H_4CH_2$ (**3a**)	**4a**/**5a**	64	82:18	>99
2	Ph (**1a**)	*p*-FC_6H_4 (**2a**)	*n*-C_5H_{11} (**3b**)	**4b**/**5b**	70	88:12	>99
3	Ph (**1a**)	*p*-$CH_3OC_6H_4$ (**2b**)	$CH_3C_6H_4C_2$ (**3a**)	**4c**/**5c**	56	90:10	>99
4	Ph (**1a**)	*p*-$CH_3OC_6H_4$ (**2b**)	*n*-C_5H_{11} (**3b**)	**4d**/**5d**	59	95:5	>99
5	Ph (**1a**)	$(CH_3)_3CCH_2$ (**2c**)	$CH_3C_6H_4CH_2$ (**3a**)	**4e**/**5e**	73	>99:1	>99
6	Ph (**1a**)	$(CH_3)_3CCH_2$ (**2c**)	*n*-C_5H_{11} (**3b**)	**4f**/**5f**	75	>99:1	>99
7	thienyl (**1b**)	$(CH_3)_3CCH_2$ (**2c**)	$CH_3C_6H_4CH_2$ (**3a**)	**4g**/**5g**	64	>99:1	>99
8	thienyl (**1b**)	*p*-$CH_3OC_6H_4$ (**2b**)	*n*-C_5H_{11} (**3b**)	**4h**/**5h**	65	>99:1	>99
9	Me (**1c**)	*p*-$CH_3OC_6H_4$ (**2b**)	*n*-C_5H_{11} (**3b**)	**4i**/**5i**	16[g]	93:7	50
10	Ph (**1a**)	*p*-FC_6H_4 (**2a**)	Allyl (**3c**)	**4j**/**5j**	67	95:5	>99
11	Ph (**1a**)	*n*-C_5H_{11} (**2d**)	$CH_3C_6H_4CH_2$ (**3a**)	**4k**/**5k**	0		
12	Ph (**1a**)	$(CH_3)_3CCH_2$ (**2c**)	*p*-$CH_3OC_6H_4$ (**3d**)	**4l**/**5l**	45	81:19	*h*

[a] The reactions were performed according to the general procedure described in ref 9. [b] Mixture of diastereoisomers. [c] Isolated yields after flash chromatography purification. [d] Determined by LC/MS and GC analysis. [e] Determined by NOESY experiments on **4a**, **4d**, **4e**, **4f**, **4i**, and **4l**. The stereochemistry of the resulting compounds was tentatively assigned according to the general trend. [f] The reactions were carried out in parallel (0.2 mmol scale). After an aqueous workup, purification was achieved by using PS-Isocyanate scavenger resin followed by SCX IEC. [g] The reaction was carried out at 60 °C. [h] Not determined due to low basicity, see ref 11.

by replacing the cyclopropanecarboxamide with a methylenecyclopropyl amide, a divergent selectivity that resulted in both five- and six-membered heterocyclic compounds.[8] The use of methylenecyclopropyl amides other than the *N*,*N*-diphenyl amide was reported to give inferior results. In contrast to those reports our objectives were to use a diverse set of cyclopropyl ketones, but most importantly to assemble the aldimines **Ib** in situ from the corresponding aldehydes and amines. Thus, addition of all three components simultaneously would give an efficient and practical method for the synthesis of compounds with three diversity points.

Scheme 1. MgI_2 Promoted Three-Component Reaction



In this Letter, we now report the development of a novel three-component MCR via an MgI_2 or Et_2AlI induced ring expansion of cyclopropyl ketones, amines, and aldehydes leading to substituted pyrrolidines. This one-step MCR strategy linked together with modern high-throughput workup and purification technologies gave an efficient protocol for library synthesis of drug-like molecules with high purity.

Our studies began with an initial multivariate screen of metal iodides (ScI_3, ZnI_2, MgI_2, Et_2AlI, and TMSI), solvents (toluene, CH_2Cl_2, hexane, THF, and acetonitrile), and reaction temperatures (rt, 50 °C, and at reflux). MgI_2 in THF or acetonitrile at elevated temperatures and Et_2AlI in all tested solvents at rt or at 50 °C gave promising results, regarding yields and purities. Further optimization revealed MgI_2 in THF at 80 °C and Et_2AlI in THF at ambient temperature to be the superior reaction conditions for the respective metal iodide.

To investigate the scope and limitations of the MgI_2 induced three-component reaction, cyclopropyl ketones **1a**−**c** were reacted with aldehydes **2a**−**d** and amines **3a**−**d** according to a general experimental procedure extracted from results given by the initial screen (Table 1).[9] The optimum reaction temperature turned out to be 80 °C for aromatic cyclopropyl ketones **1a** and **1b**, while cyclopropyl methyl ketone (**1c**) gave higher yields of **4i**/**5i** and cleaner reactions by decreasing the reaction temperature to 60 °C. The chosen reaction time of 6 h was a tradeoff to get a unified procedure. With most combinations, the reactions were completed within 3 h. However, when using e.g. *p*-methoxybenzaldehyde (**2b**) longer reaction times were needed for completion, >10 h. Extended reaction times on the other hand decreased the

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yields and increased the number and amount of unidentified byproducts according to analytical LC/MS, and this was especially pronounced for reaction times longer than 18 h.

Except for linear aliphatic aldehydes (e.g. **2d)**, most of the tested aldehyde and amine combinations, together with the cyclopropyl phenyl ketone **1a**, gave acceptable yields of products (56−75%) (Table 1, entries 1−6). The highest yields were observed with the aliphatic aldehyde **2c** (entries 5 and 6). The use of the electron-rich *p*-methoxybenzaldehyde **2b** gave lower yields than the electron-deficient *p*-fluorobenzaldehyde **2a** (entries 1−4).

Unsatisfactorily, in contrast to the branched aldehyde **2c** (entries 5−7 and 12), the linear aliphatic aldehyde **2d** resulted in little or no yield of the desired products (entry 11) and the HPLC trace showed a multitude of byproducts. A tentative explanation for this unexpected trend may be based on the imine−enamine equilibrium. If the equilibrium is shifted toward the enamine, an increased number of byproducts could result via additional reaction pathways, e.g. enamine to imine addition generating polymeric material. Increased branching in the aliphatic chain of the aldehyde increased the yield of the desired product (isopropanal gave 32% isolated yield of the corresponding pyrrolidine), whereas an increase/decrease in chain lengths, e.g. *n*-pentanal/*n*-propanal, had no beneficial effect; in both cases no product was formed.

Furthermore, the diastereomeric product distribution was significantly influenced by the aldehyde. Using aromatic aldehydes **2a** and **2b** resulted in *anti*:*syn* ratios of between 80:20 and >99:1, while the aliphatic aldehyde **2c** gave the anti isomer exclusively (*anti*:*syn* >99:1). On the other hand, the amines used in those examples seemed to have little or no influence on the observed variations in diastereoselectivities. Exchanging the phenyl group in ketone **1a** with a heteroaromatic ring, e.g. thienylcyclopropyl ketone (**1b**), had little impact on the result (compare entries 4 and 5 with 7 and 8). Disappointingly, the aliphatic cyclopropyl methyl ketone **1c** gave a sluggish reaction under the standard conditions. Lowering the temperature to 60 °C resulted in a cleaner reaction, but still with a low yield (entry 9). Although not perfect, this could nevertheless be useful for library synthesis considering that a one-step procedure is used to obtain a rather advanced end product. Both the allylic amine (**3c)** and *p*-anisidine (**3d**) (entries 10 and 12) worked well in the reaction, affording the products **4i**/**5i** and **4l**/**5l** respectively in moderate to good yields. Together with benzylic amines (i.e. **3a**), these amines (**3c** and **3d**) form pyrrolidines with potentially cleavable *N*-substituents previously proven to be useful as *N*-protection groups.[10] In addition, anilines such as *p*-anisidine (**3d**) result in products with low basicity, which is interesting from a diversity perspective.[11]

Although the mechanism for this three-component reaction has not yet been thoroughly investigated, a few comments can be made regarding the use of MgI_2. An assumption was that 1 equiv of MgI_2 was consumed in the formation of the aldimine (**Ib**)[12] and that a catalytic amount of MgI_2 was needed for the ring expansion reaction to proceed. Decreasing the amount of MgI_2 to 0.8 equiv slowed the reaction and stopped it before completion. It was interesting, however, that substoichiometric amounts of MgI_2 still gave reasonable amounts of products. Increasing the amount of MgI_2 to 1.5 equiv gave no improvements compared to 1.0 equiv nor did an increase in the added amounts of aldehyde and amine (1.5 equiv) to form the aldimine.

To streamline this protocol for the synthesis of compound libraries, a fast and efficient purification is essential. After an extractive workup, purification was achieved with PS-Isocyanate scavenger resin (to capture excess amine) and SCX IEC. The purities and diastereomeric ratios of the compounds in Table 1 (0.2 mmol scale) were determined by LC/MS (UV) and GC, respectively. These results clearly show the efficiency of this sequence. The crude UV purities were between 53% and 90% and after workup and purification they all increased to >99%, indicating that the protocol is very adaptable to library production.

It was also possible to reduce the reaction time considerably by performing the reactions in a microwave oven. The combination with **1a**, **2c**, and **3b** gave the same result after 5 min (160 °C, 100 W) as after 6 h with standard conditions (Table 1, entry 6).

Et_2AlI, the other efficient metal iodide found in the initial screen, gave comparable results with the MgI_2 induced protocol but with some important differences (Table 2).[13]

Table 2. Et_2AlI Promoted Three-Component Reaction

entry	product[a]	yield[b] (%)	dr[c] (anti:syn)	purity[d] (%)
1	**4a/5a**	70	85:15	96
2	**4b/5b**	50	72:28	98
3	**4c/5c**	54	93:7	84
4	**4d/5d**	15	91:9	95
5	**4e/5e**	42	99:1	98
6	**4f/5f**	55	>99:1	98
7	**4g/5g**	57	>99:1	98
8	**4h/5h**	35	94:6	85
9	**4j/5j**	24	83:17	>99
10	**4k/5k**	57	>99:1	81

[a] Mixture of diastereoisomers. [b] After a parallel purification (0.2 mmol scale) by PS-Isocyanate scavenger resin and IEC with SCX cartridges. [c] Determined by NOESY experiments on **4a**, **4d**, **4e**, **4f**, **4i**, **4**l, and **4k**. The stereochemistry of the resulting compounds was tentatively assigned according to the general trend. [d] Determined by LC/MS (UV) analysis.

Several of the combinations of cyclopropyl ketone, aldehyde, and amine used in the MgI_2 examples were repeated with

(9) **General procedure for the MgI_2-promoted three-component synthesis of substituted pyrrolidines:** The aldehyde (1.0 mmol; 1.0 equiv), MgI_2 (1.0 mmol; 1.0 equiv), and cyclopropyl ketone (1.0 mmol; 1.0 equiv) were added sequentially to a solution of the amine (1.0 mmol; 1.0 equiv) in THF (4 mL) at rt, and the resulting mixture was shaken at 80 °C. After 6 h, the reaction was cooled to ambient temperature and quenched with a saturated aqueous $Na_2S_2O_3$ solution (2 mL). The mixture was extracted with EtOAc (5 mL) and the organic phase was washed with a saturated aqueous $NaHCO_3$ solution (2 mL) and brine (2 mL), dried over Na_2SO_4, filtered, and concentrated. The corresponding crude reaction mixture was purified by flash chromatography (CH_2Cl_2 + MeOH 1%) or by PS-Isocyanate scavenger resin followed by an IEC, which afforded the pure compound in reasonable yield.

Et_2AlI to give yields between 15 and 70% and purities between 81 and 99% after a workup purification sequence containing extraction, treatment with PS-Isocyanate scavenger resin, and an IEC. Comparison with the MgI_2 promoted reactions indicated comparable diastereomeric ratios, ranging from *anti*:*syn* 72:28 to >99:1. A major difference was the reagent combination with the linear aliphatic aldehyde **2d**. While the MgI_2 promoted reaction did not result in any product (Table 1, entry 11), the use of Et_2AlI gave the desired product in 57% yield (Table 2, entry 10). The lower temperature could be the beneficial factor in this outcome.

Most noteworthy is the robustness of the chemistry: all reagents were used as purchased and no special precautions such as predrying vials or using an inert atmosphere were needed. The protocols were mainly aimed for library synthesis and therefore no individual reaction conditions were optimized.

In summary, we have reported a novel MgI_2 or Et_2AlI promoted three-component reaction between cyclopropyl ketones, aldehydes, and amines resulting in the formation of substituted pyrrolidines. With use of either of the two developed protocols, most combinations of aliphatic/aromatic aldehydes, cyclopropyl ketones, and primary amines were compatible as reaction partners. The presented protocols are practical and efficient and are therefore readily amenable for library synthesis. A full account will be presented in due course.

Acknowledgment. We thank Tina Jensen for HPLC analyses, Jakob Strange Ebbesen for pK_a measurements, and Professor David Tanner and Dr. Nicholas Kelly for valuable comments on the manuscript.

Supporting Information Available: General experimental procedures and compound characterization (HRMS, ^{1}H NMR, ^{13}C NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) The pK_a values for **4f** and **4l** were experimentally determined as 8.53 and 6.60, respectively.

(12) Lewis acids are known to promote the formation of imines, e.g.: (a) White, W. A.; Weingarten, H. *J. Org. Chem*. **1967**, *32*, 213. (b) Billmann, J. H.; Tai, K. M. *J. Org. Chem*. **1958**, *23*, 535. (c) Texier-Boullet, F. *Synthesis* **1985**, 679.

(13) The same general procedure as in the MgI_2 promoted reaction was followed, with the exceptions of using 1.5 equiv of Et_2AlI at rt (see Supporting Information). The 25% Et_2AlI solution in toluene is easier to handle, and since the reaction can be performed at rt, this makes Et_2AlI protocol more useful when it comes to automation and library synthesis.